Arnold B. Calmann (abc@saiber.com)
Geri L. Albin (gla@saiber.com)
SAIBER LLC
One Gateway Center
10th Floor, Suite 1000
Newark, New Jersey 07102
Telephone: (973) 622-3333
Facsimile: (973) 622-3349

Of Counsel
William A. Rakoczy (wrakoczy@rmmslegal.com)
Paul J. Molino (paul@rmmslegal.com)
Tara M. Raghavan (traghavan@rmmslegal.com)
Luke T. Shannon (lshannon@rmmslegal.com)
RAKOCZY MOLINO MAZZOCHI SIWIK LLP
6 West Hubbard Street, Suite 500
Chicago, Illinois 60654
Telephone: (312) 222-6301
Facsimile: (312) 222-6321

Attorneys for Defendants
Apotex Inc. and Apotex Corp.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

BRISTOL-MYERS SQUIBB COMPANY, Plaintiff, v. APOTEX INC. and APOTEX CORP., Defendants.	Civil Action No. 3:10-cv-5810 (MLC) (LHG) (consolidated with Civil Action No. 3:11-cv-6918 (MLC) (LHG))

APOTEX INC. AND APOTEX CORP.'S RESPONSIVE
CLAIM CONSTRUCTION BRIEF PURSUANT TO L. PAT. R. 4.5

TABLE OF CONTENTS

TABLE OF AUTHORITIES

FEDERAL CASES

FEDERAL STATUTES

FEDERAL REGULATIONS

OTHER AUTHORITIES

Defendants Apotex Inc. and Apotex Corp. ("Apotex") respond to Plaintiff BMS's May 4, 2012 claim construction briefing relating to the asserted claims of the patents-in-suit[1] as follows.

I. INTRODUCTION.

For a number of claim terms, BMS asserts non-constructions, *e.g.*, "[claims are] readily understandable to one of ordinary skill and do not require construction by the Court" or have meanings "clearly set forth in the specification or other intrinsic evidence." (BMS Opening Br. at 2). BMS's refusal to articulate specific meanings for various claim terms in its opening brief should be deemed a waiver, with Apotex's proposed constructions adopted. For other claim language, BMS proposes constructions that lack clarity; conflict with explicit disclosures in the intrinsic record; or do not, in fact, reflect the understanding of one of ordinary skill in the art.

Separately, BMS's attacks on Apotex's motives are unfounded and unproductive. (BMS Opening Br. at 2). The Local Patent Rules are intended to encourage parties to raise claim construction disputes earlier rather than later. Thus, as Apotex's opening brief explained, save for claim language that BMS left insolubly ambiguous and indefinite during prosecution, Apotex proffers ordinary meanings for claim terms. For those instances where the intrinsic evidence alters ordinary meaning via specific claim language, lexicography, and/or subject-matter surrender under Federal Circuit caselaw, Apotex deferred to the specific claim language.

II. ANALYSIS OF CLAIM TERMS IN DISPUTE.

A. Claim Terms of the Asserted '746, '875, and '856 Molecule Patents

1. "Salts[s]"/"Compound" ('746 patent, claims 6, 7; '875 patent, claims 1, 2, 3, 11, 27).

BMS approves of giving the Molecule patent terms "salts" and "compound" their plain

[1] "Patents-in-suit" refers to U.S. Patent Nos. 6,596,746 ("the '746 patent"), 7,125,875 ("the '875 patent"), 7,153,856 ("the '856 patent"), and 7,491,725 ("the '725 patent"). As in its Opening Brief, Apotex refers to the '746, '875, and '856 patents collectively as the "Molecule patents."

and ordinary meaning, but gives this Court no legal rationale that justifies ignoring the explicit specification definitions given for "salts" and "compound" in the Molecule patents. That is because it cannot. *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1379 (Fed. Cir. 2009) ("When a patentee explicitly defines a claim term in the patent specification, the patentee's definition controls."). The purported inventors defined these terms; BMS must live with the definitions the purported inventors chose. BMS does not dispute Apotex's proposed construction mirrors these specification definitions, in which the term "salt(s)" includes both zwitterions and quaternary ammonium salts, and the term "compound" includes salts. (*See, e.g.*, D.I. 1-2, '746 patent at col. 6, ll. 17-31).

BMS's own expert Dr. Jorgensen effectively sides with Apotex. When asked about the specification definition provided for "salt(s)," Dr. Jorgensen characterized this definition as "a totally normal definition of salt." (Shannon Supp. Decl., Ex. A, Jorgensen Tr. 42:19-20). Dr. Jorgensen went further to state that "the term 'salt,' you know, is well understood by a person of ordinary skill to mean what's being described [by the purported inventors in the '746 patent at col. 6, ll. 21-31], and that would apply to the claim where it says salt." (Shannon Supp. Decl., Ex. A, Jorgensen Tr. 43:16-20). In short, even BMS's expert agrees that there is no reason to reject the specification's definition for "salts."

2. "*A compound* or salt thereof selected from the group *consisting of*." ('746 patent claim 6).

BMS admits that "[t]he phrase 'selected from the group consisting of' is a well accepted form of alternative expression commonly referred to as a Markush group, which limits the claimed 'compound or salt thereof' to the compounds enumerated in the list of compounds and/or salts recited in claim 6." (BMS Opening Br. at 5) (citing MPEP § 2173.05(h)). But BMS then promptly disregards the legal significance of the claim scope that results from this format as

a matter of law in order to broaden the claim scope. BMS's observation that the specification at some point purported to enumerate "*compositions* of the present invention" obfuscates, rather than clarifies, the meaning of "*compounds* … consisting of" the specified list of chemical names.

BMS's expert Dr. Jorgensen admitted at deposition that one of ordinary skill understands "compounds" differ from "compositions," and are not equatable. (*See* Shannon Supp. Decl., Ex. A, Jorgensen Tr. 28:11-17 ("Q. Is the word 'composition' different than the word 'compound'? A. Yes. Yes. Compound can be a single molecular entity. A composition could be a molecular entity such as an API, again, active pharmaceutical ingredient, with other additives.").

BMS's suggestion that its compound list really covers any composition that contains a listed compound—even though claims besides claim 6 expressly use the term "composition" and not "compounds"[2]— also ignores the doctrine of claim differentiation. *See, e.g.*, *Leibel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 899, 910 (Fed. Cir. 2004) ("[T]he presence of a dependent claim that adds a particular limitation raises a presumption that the limitation in question is not found in the independent claim.").

The cases BMS relies on do not justify a further expansion of its actual "compound … consisting of" claim language to the broader construction that would permit any composition that mixed in one or more compounds from the list to fall within the scope of the claim language. But that is not legally permissible, and the Federal Circuit has left no doubt on this point:

> [A]lthough "a" without more generally could mean one or more in an open-ended patent claim "a" with "consisting of" in this case indicates only one member of a Markush group. If a patentee desires mixtures … the patentee would need to add qualifying language while drafting the claim. Thus, without expressly indicating the selection of multiple members of a Markush grouping, a patentee does not claim anything other than the plain reading of the closed claim language.

[2] (*See, e.g.*, D.I. 1-2, '746 patent at col. 302, ll. 5-8 (claiming a composition "comprising a pharmaceutically acceptable vehicle or diluent and at least one compound of claim 6")).

Abbott Labs. v. Baxter Pharm. Prods., Inc., 334 F.3d 1274, 1281 (Fed. Cir. 2003). The purported inventors chose to use the term "*a* compound from the group *consisting of*" in claim 6, and so *Abbott* mandates that claim 6 is closed to other compounds not listed in that claim. BMS cites *Teva Pharm. USA, Inc. v. Amgen, Inc.*, No. 09-5675, 2010 U.S. Dist. LEXIS 95288, at *20-*21 (E.D. Pa. Sept. 10, 2010), to suggest that claim 6 can cover more compounds than are disclosed in claim 6. (BMS Opening Br. at 6). *Teva* is unhelpful to BMS because the district court rejected Teva's assertion that the "consisting of" claim language should be construed to include impurities. *Id*. at *25 ("Amgen's construction is correct. The entire basis of the patent is … a 174-amino acid species that is 'entirely free' of the 177-amino acid species").

Other courts have consistently followed the *Abbott* logic, which is all that Apotex asks this Court to do. *See, e.g.*, *Green Edge Enters., LLC v. Rubber Mulch Etc., LLC*, No. 02-566, 2007 WL 1566485, *4 (E.D. Mo. 2007) (finding that "the Markush groups are closed and that they do not contain any qualifying language which would allow mixtures or combinations"); *Dow Agrosciences LLC v. Crompton Corp.*, 03-654, 2004 WL 1087362, at *7 (S.D. Ind. 2004) ("Therefore, in our case, the language 'at least one' and 'chosen from the group consisting of' in our judgment modifies the word substituent, allowing the patentee to select more than one substituent from among the Markush group."). Like *Green Edge* and unlike *Dow*, claim 6 contains no qualifying language allowing that claim to capture more than one compound listed, mixtures of compounds listed, or compounds not listed.

Conoco, Inc. v. Energy & Environ. Int'l, 460 F.3d 1349, 1360 (Fed. Cir. 2006), and *Novo Nordisk v. Eli Lilly Co.*, 1999 WL 1094213, at *13 (D. Del. Nov. 18, 1999), do not support BMS either. BMS cites these cases for the proposition that "in the context of chemical patents 'consisting of' does not exclude impurities." (BMS Opening Br. at 7). Neither case holds so

broadly. In both, the claim language at issue—"selected from the group consisting of water and water-alcohol mixtures" in *Conoco*, "or a mixture of m-cresol and phenol" in *Novo Nordisk*—expressly contemplated mixtures.[3] Claim 6 does not. Neither *Conoco* nor *Novo Nordisk* addresses Markush claims that propound an extensive list of specific chemical names, and neither of these cases should be read to negate *Abbott*, as BMS suggests.

BMS wants the "impurity" language implied in its construction because BMS does not want to highlight that multiple compounds in the claim 6 list will readily exist in mixtures with one another. BMS thus seeks an "impurity" exception that would effectively permit claim 6 to cover multiple compounds on the list mixed together (*e.g.*, the same compound as a salt or as its non-salt structure). BMS had the opportunity to draft claim 6 to cover "mixtures," and chose not to. It cannot use an impurity carve-out as an excuse to expand the claims to cover mixtures, such as samples containing multiple compounds listed in claim 6, which would conflict with *Abbott*.[4]

Dr. Jorgensen's opinions do not support BMS either. Dr. Jorgensen freely admitted that his claim 6 opinions do not account for the legal significance of transitional phrases such as "consisting of," or "comprising," concepts he was unfamiliar with. (Shannon Supp. Decl., Ex. A, Jorgensen Tr. 63:14-20). Dr. Jorgensen was unaware that the use of "comprising" versus

---

[3] *Novo Nordisk*, 1999 WL 1094213, at *13, cited two cases relating to impurities, *Sakano v. Rutemiller*, 158 U.S.P.Q. 47, 51 (Bd. Pat. Interf. 1968), and *Ex Parte Davis*, 80 U.S.P.Q. 448, 450 (Bd. App. 1948). In *Sakano*, the claim terms "alloy" and "aluminum" were recognized as inherently containing known impurities; in *Davis*, the claim language at issue was "consisting essentially of," which has long been construed as permitting other components not material to invention performance. Such scenarios are inapplicable here.

[4] BMS implies that it is acceptable for claim 6 to cover compositions with impurities by arguing that "[a] person of ordinary skill in the art would understand it is *impossible* to have a compound that is 100% free of impurities." (BMS Opening Br. at 7) (emphasis added). But that position is belied by the '725 patent, which calls its purported invention "substantially pure," which is explicitly defined as "a compound having a purity greater than 90 percent, including … 100 percent." (D.I. 1-5, '725 patent at col. 15, ll. 26-30). To the extent that BMS now believes that the existence of a compound "100% free of impurities" is "impossible," then by the same token its claims of the '725 patent cover subject matter that is unsupported, inoperative, and invalid.

"consisting of" in patent claims influences the scope of claim 6: "Q. In the context of a patent claim or specifically claim 6 [of the '746 patent], do you understand what the—specifically what the word 'consisting of' means? A. Yes. Q. Would claim 6 be different if it used the term 'comprising'? A. To a person of ordinary skill, I would say no." (Shannon Supp. Decl., Ex. A, Jorgensen Tr. 64:22 – 65:6). BMS cannot justify its claim construction position using expert opinions that fail to account for proper legal standards.

3. Chemical names identified in claim 6 such as "'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecaroxamide." ('746 patent claim 6).

When it comes to deciphering the chemical language set forth in claim 6, Apotex's proposed construction is the plain and ordinary meaning of this chemical language as established by the IUPAC Guidelines. BMS seeks to equate structures with chemical names but skirts the issue of what naming convention to follow and instead groundlessly proclaims that this term should be understood to encompass compounds illustrated by several structures not provided by claim 6, without reference to a standard nomenclature. BMS provides no basis for including actual structures into the meaning of this term, in disregard of whether the structures it proffers actually correspond to the chemical language in the claims.

BMS's primary argument is that "there are several naming conventions used in the art," and that Apotex "erroneously assumes the IUPAC nomenclature guidelines [are] the only way in which a compound can be named." (BMS Opening Br. at 8). But this begs the question: what alternative naming convention(s) does BMS contend could apply, besides IUPAC, that would produce a structural outcome different from that resulting from the IUPAC guidelines? BMS does not say, because BMS cannot dispute that IUPAC provides the foremost naming convention and is seen as authoritative by those of ordinary skill in the art. Its own expert recognized as much. (*See* Shannon Supp. Decl., Ex. A, Jorgensen Tr. 88:21 – 89:7 ("Q. Is there a more

foremost [naming convention other than IUPAC]? A. No. Q. Is there a more authoritative convention than IUPAC? A. No. Q. Is there a clearer way to present nomenclature guidelines, particularly of complicated molecules, than the IUPAC guidelines? A. No. The IUPAC people have put more time in to worrying about this than others.")).

Neither the specification nor file history suggest an alternative naming convention. The IUPAC guidelines are, in fact, specifically referenced when describing compound isomers. (*See, e.g.*, D.I. 1-2, '746 patent at col. 7, ll. 15-17 ("The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations"); D.I. 1-3, '875 patent at col. 7, ll. 41-43; D.I. 1-4, '856 patent at col. 7, ll. 32-34). Yet, BMS presents no reason to depart from the use of the IUPAC Guidelines with respect to claim 6.

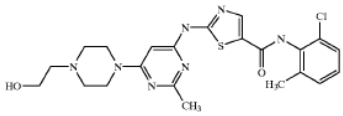
Further, the default standard for naming compounds for those of skill in the art worldwide is IUPAC's guidelines. (*See* Fernandez Supp. Decl. ¶¶ 8-9). The fact that BMS notes that some small compounds have common names does not detract from the IUPAC Guidelines' authority. The IUPAC Guidelines recognize that flexibility is allowed with respect to the nomenclature of smaller, common molecules.[5] It is understood by those in the art that for larger, complex molecules a uniform and consistent nomenclature is crucial to accurately convey a structural concept, and the IUPAC guidelines serve this purpose. (*See, e.g.*, Shannon Decl., Ex. A, IUPAC Guidelines at xiii). BMS's Dr. Jorgensen recognizes this, as he must.[6]

---

[5] (*See, e.g.*, Shannon Decl., Ex. A, IUPAC Guidelines at xiii ("… there are traditional names, semisystematic or trivial, which are widely used for a core group of common compounds…[W]here they meet the requirements of utility and precision, and can be expected to continue to be widely used by chemists and others, they are retained and, for the most part, preferred in this Guide.")).

[6] (*Id.*; *see also* Shannon Supp. Decl., Ex. A, Jorgensen Tr. 78:7 – 79:5 ("Q. With respect to complex molecules, would it be fair to say that the IUPAC guidelines are the foremost authority on naming those complex molecules? A. The IUPAC guidelines is the foremost recommendation, so I don't think there are sort of competing recommendations for naming, but

Thus, BMS has not justified construing claim 6 chemical language with non-IUPAC standards, let alone substituting the chemical language in the claim with a structural graphic.

4. The compound  **('746 patent claim 43; '856 patent claim 1).**

BMS could have explicitly shown hydrogen atoms present at the bridging nitrogen atoms in the graphical structural depiction in these claims to reflect dasatinib's true molecular structure. It failed to do so, and the lack of structural hydrogens conveys to one of ordinary skill in the art that the above structure *is not* dasatinib.

BMS asks this Court to accept that those of ordinary skill blithely add or omit hydrogen atoms on nitrogen atoms in structures, without risk of ambiguity or presumption of structural differences. (*See* BMS Opening Br. at 14). This begs the question—what other structural elements does BMS presume can be added or ignored at will? Just as BMS recognizes that compound name changes "can result in chemical structures that are illustrated in different ways, *i.e.*, with or without the hydrogen or carbon atoms explicitly shown," (BMS Opening Br. at 8), so too do structural meanings change depending on the number, type and location of hydrogens on a structure. For example, a nitrogen atom with three chemical bonds to atoms such as hydrogen (an "amine") is recognized as chemically distinct from a nitrogen atom involved in four chemical bonds (an "ammonium"). (Fernandez Supp. Decl. ¶ 11).

BMS's expert Dr. Jorgensen does not claim that the person of ordinary skill would find *no* chemical difference between nitrogen atoms with either 2, 3 or 4 bonds to hydrogen atoms. He instead suggests that since the specification does not always fill nitrogen atoms in chemical

---

there are little differences, like I said, in—that nobody cares about.… Q. So, even if, according to the IUPAC guidelines, there is one specific name, there's flexibility in those guidelines, so that you could use perhaps a more common name or a more traditional name? A. Yes.")).

structures with hydrogen atoms, one should simply presume they were meant to be there. (*But compare* D.I. 51, Joint Statement, Ex. D, ¶ 4, *with* Shannon Supp. Decl., Ex. A, Jorgensen Tr. 180:22 – 181:7). The problem with Dr. Jorgensen's presumption is that the specification shows a variety of structures with bridging nitrogen atoms, some with a hydrogen atom visually present, and others without. The person of ordinary skill would not presume the decision to include or exclude the structural hydrogens was meaningless or unambiguous; one of ordinary skill in the art would conclude that where no hydrogen is shown, the absence of a hydrogen atom was intentional. (*See* Fernandez Supp. Decl. ¶ 25).

The extrinsic evidentiary support Dr. Jorgensen offers is not persuasive. Dr. Jorgensen cites a handful of non-authoritative sources which he claims show that those of ordinary skill in the art may or may not explicitly show hydrogen atoms graphically on nitrogen atoms. Dr. Jorgensen's reasoning is flawed. In all of the patent sources Dr. Jorgensen cites, the figures without hydrogen atoms bonded to a nitrogen atom are intermediate structures intended to reflect that many undefined and/or variable substituents potentially could be present. One of ordinary skill would recognize that these generic figures were merely a guide and not intended to define a final, individual compound structure as in claim 43 of the '746 patent and claim 1 of the '856 patent. (Fernandez Supp. Decl. ¶¶ 15-16; id. at ¶¶ 26-31 (discussing error in WO 2008/070350)).

By contrast, the structure in claim 43 of the '746 patent and claim 1 of the '856 patent **is** a final, claimed compound. Rather than clarifying ambiguities by showing hydrogen bonded to the bridging nitrogen atoms—which is what BMS could have tried to do if its goal was to claim dasatinib—it chose to pursue a claim that lacked a hydrogen atom on the bridging nitrogen.

Other references Dr. Jorgensen cites support Apotex's position. Dr. Jorgensen refers to several printouts from a PubChem website. PubChem itself recognizes that ambiguities result

where hydrogen atoms are not explicitly shown, which is why PubChem provides explicit instructions to users of its structure search function to explicitly show all hydrogen atoms:

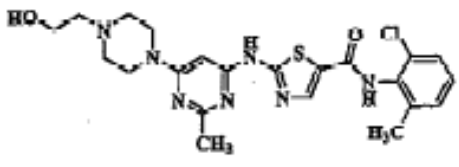
> Please note that if explicit hydrogen atoms are not provided in the chemical structure query, PubChem will use the most likely valence state for the atoms in the provided chemical structure. ***To achieve desired and consistent results, it is best to provide all explicit hydrogens in chemical structure queries of this search type***."

(Shannon Supp. Decl., Ex. D) (emphasis added).

BMS's alternative theory that the PTO has already "determined" that claim 43 claims dasatinib is unsupported. Nowhere does BMS suggest a PTO Examiner made this finding during prosecution. Nor did the PTO perform this analysis for claim 43 of the '746 patent in BMS's application for patent term extension. ***BMS*** provided the PTO with a self-serving statement that claim 43 covers dasatinib as part of its application for a patent term extension. Under the applicable regulations, the PTO makes patent term extension decisions based solely on "the representations contained in the application for extension." 37 C.F.R. § 1.750; *see also* 37 C.F.R. § 1.765(a) (insisting that the duty of candor and good faith towards the PTO applies to these applications, and mandating disclosure of any "material information adverse to a determination of entitlement to the extension sought").

More specifically, when BMS represented to the PTO that claim 43 covers dasatinib, BMS misstated what claim 43 actually covered, replacing the claim 43 structure with the dasatinib structure containing hydrogen atoms bonded to the bridging nitrogen atoms:

(g) Dasatinib is covered by independent claim 43 of U.S. Patent 6,596,746 which claims the



same compound, including salts thereof.

(D.I. 62, Attachment 2, Gannon Decl., Ex. D, at 4). BMS never provided the PTO with a side-

by-side comparison of the actual claim 43 structure and dasatinib's structure, or otherwise alerted the PTO to the missing hydrogens. The above representation to the PTO demonstrates that BMS knew full well the material importance of the hydrogen atoms on nitrogen to define the dasatinib structure. Since the PTO relied upon BMS's false misrepresentation that claim 43 covers BMS's Sprycel® product, BMS's cries for deference to the PTO ring hollow.

The inescapable conclusion is that if the goal of claim 43 of the '746 patent and claim 1 of the '856 patent was to claim the dasatinib structure, BMS knew how to do it with the appropriate addition of hydrogen atoms to the bridging nitrogen atoms, and chose not to. If BMS wants to ask the PTO for amended claims (*e.g.,* via a reissue application), BMS can try to do so, but cannot now rewrite its claims under the guise of claim construction.

5. "Administering to"; "A subject in need thereof" ('746 patent claims 7, 44, 47; '856 patent claim 1; '875 patent claims 1, 2, 3, 11, 27).

BMS's attempts to justify its proposed construction of "administering to" and "a subject in need thereof" in fact highlight the appropriateness of Apotex's constructions.

a. "A subject in need thereof" ('746 patent claims 7, 44, 47; '856 patent claim 1; '875 patent claims 1, 2, 3, 11, 27).

BMS purports to rely on a line in the specification as defining the term "a subject in need thereof," arguing that "[t]he patent states that '***[p]referred*** subjects for treatment include animals ….'" (BMS Opening Br. at 11) (emphasis added) (quoting '746 patent at col. 26, ll. 53-57). The Federal Circuit has repeatedly held that statements of preference in the specification are not presumptively definitional. *See, e.g.*, *Liebel-Flarsheim*, 358 F.3d at 913 ("[I]t is improper to read limitations from a preferred embodiment described in the specification—even if it is the only embodiment—into the claims absent a clear indication in the intrinsic record that the patentee intended the claims to be so limited."); *Rhine v. Casio, Inc.*, 183 F.3d 1342, 1346 (Fed.Cir.1999) (declining to construe claims as limited to preferred embodiment); *Laitram Corp.*

v. Cambridge Wire Cloth Co., 863 F.2d 855, 865 (Fed. Cir. 1988) ("References to a preferred embodiment, such as those often present in a specification, are not claim limitations.") The claims containing this term are not limited to "animals," and so construction of this term should not import this limitation from the specification.

BMS also fails to provide any construction that accounts for the fact that the "subject" must be "in need thereof" but instead claims that Apotex does not identify intrinsic evidence to support its construction. BMS apparently believes that because Apotex does not cite chapter and verse the patents or prosecution history for an explicit definition of "in need thereof" that this term cannot require that a second party (*e.g.,* a physician) to diagnose the subject as being susceptible to treatment. BMS is wrong.

As Apotex explained in its Opening Brief, the obvious prerequisite to administering the disclosed compounds to "a subject in need thereof" is that the subject must be known to require such treatment. *See, e.g., Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329 1331-33 (Fed. Cir. 2003) (a method of treating requires the "need" for therapy to be recognized and appreciated); *Schering Corp. v. Glenmark Pharm. Inc.*, No. 07-1334 (JLL), 2008 WL 4307189, at *9 (D.N.J. Sept. 16, 2008) (term "in need of such treatment" requires intent to use the drug for the purpose for which it was intended). One of ordinary skill in the art would understand from the specifications of the patents-in-suit given the nature of the diseases involved that the contemplated treatments are not those amenable to self-diagnosis by the lay person. The claims are directed to compounds that purportedly can be used for the treatment of protein tyrosine kinase-related disorders. Thus, a "subject in need thereof" must be someone known to be suffering from such a disorder, which depends entirely on whether a physician, clinician, etc., has diagnosed the subject as such. Apotex's proposed construction thus is simply a logical

understanding of the term "a subject in need thereof" given the nature of the disease at issue.

b. "Administering to" ('746 patent claims 7, 44, 47; '856 patent claim 1; '875 patent claims 1, 2, 3, 11, 27).

Instead of giving meaning to the term "administering to," BMS's construction fails to clarify anything. BMS cites its hand-picked dictionary extrinsic evidence source, which defines "administer" as "to mete out" or "to give remedially." (BMS Opening Br. at 9) (citing Merriam-Webster's Collegiate® Dictionary at 15 (10th ed. 1993)). But "to give remedially" and "to mete out" likewise contemplates two actors, *i.e.*, the giver and receiver, and thus does not undermine Apotex's two-participant point.

BMS argues Apotex's construction must be invalid absent explicit language in the intrinsic record that two actors participate in the "administering to" step. (*See* BMS Opening Br. at 10). But a patent specification "need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). One of ordinary skill readily understands the requirement of two actors as a necessary logical inference in view of the operation of this term. *See Eastman Kodak Co. v. Goodyear Tire & Rubber Co.*, 114 F.3d 1547, 1553-54 (Fed. Cir. 1997), *abrogated on other grounds by Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448 (Fed Cir. 1998) (construing "to" by "examin[ing] principally the claim language and any syntactic signs of its meaning"). "Administering to" requires two participants: the administrator, and the recipient. Indeed, if BMS had wanted to craft this claim to cover single-party acts, it easily could have done so, as the Federal Circuit has recognized. *See BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1381 (Fed. Cir. 2007).

The case law BMS cites is inapposite. (*See* BMS Opening Br. at 10) (citing *Purdue Pharma L.P. v. Endo Pharm., Inc.*, 438 F.3d 1123, 1136-37 (Fed. Cir. 2006); *Aventis Pharma S.A. v. Hospira, Inc.*, 2012 U.S. App. LEXIS 7095, at *7 (Fed. Cir. April 9, 2012);

Decisioning.com, Inc. v. Federated Dep't Stores, Inc., 527 F.3d 1300, 1313 (Fed. Cir. 2008)). Those cases stand for the uncontroverted black letter law that a court should not import claim "limitations" where not required by the claim language, specification, or prosecution history. Here, the intrinsic meaning of the language used mandates two participants. Apotex's proposed construction is consistent with the plain meaning of the claim language itself.

BMS's citation to *Accorda Therapeutics Inc. v. Apotex Inc.*, 08-4937, 2011 WL 4074116 (D.N.J. Sept. 6, 2011), is likewise unhelpful. (*See* BMS Opening Br. at 9). In that case, claim construction was not at issue, and the court was faced with determining whether to address method of treatment claims within the multiple-party infringement framework. *Id*. at *27. To the extent *Accorda* applies at all, it supports Apotex's construction. The *Accorda* court reasoned that "a doctor could perform the administering of a therapeutically effective amount of tiznidine with food as well as administration of the composition, thereby reducing somnolence in a patient. The patient could read the label, request the capsules from his doctor, and subsequently practice the claimed method." *Id*. Under both of these scenarios, the patient *and* the doctor are necessary actors—just as Apotex's construction recognizes.

6. "Wherein the cancer is resistant to [treatment by] STI-571." ('875 patent claims 9, 10, 12, 27).

BMS offers an improper construction of the term "wherein the cancer is resistant to treatment by STI-571" by rewriting "is resistant to" as, "exhibits resistance to." BMS relies solely on extrinsic evidence, namely its dictionary of choice, which defines "resistant" as "giving or capable of resistance." (BMS Opening Br. at 17) (citing Merriam-Webster Collegiate® Dictionary at 1564 (1998)). BMS fails to articulate how its definition could possibly be helpful to the Court in construing this term. In reality, BMS's construction is an inappropriate attempt to broaden the scope of this term through claim construction.

By specifying that the cancer "is resistant to treatment," the claim is clear that the cancer being treated is just that—it is resistant to treatment. A cancer that "exhibits resistance" to treatment implies the cancer could simultaneously have its susceptibility to treatment merely diminished to some undefined degree. In this way at least, BMS's proposed construction is broader than the "is resistant to" language used in this term. Moreover, because such a construction leaves unanswered how one of ordinary skill in the art is to measure the extent to which a cancer must "exhibit resistance to" STI-571 in order to fall within this meaning of this term, BMS's proposed construction is indefinite and thus invalid.

By contrast, Apotex's proposed construction provides clarity and reflects the meaning the purported inventors intended. As Apotex explained in its opening brief, the '875 patent makes clear that its claims are intended to cover compounds purportedly useful in the treatment of cancers resistant to, for example, Gleevec®, also known as STI-571. (D.I. 1-3, '875 patent at col. 28, ll. 35-38). The only way one of ordinary skill in the art could know whether this limitation is met is to know beforehand whether the subject suffers from a cancer that is resistant to STI-571. *See, e.g., Jansen*, 342 F.3d at 1331-33 (requiring the need for therapy to be recognized); *Schering*, 2008 WL 4307189, at *9. And only a physician can determine whether the subject suffers from such a cancer. Apotex's proposed construction simply recognizes this.

B. Claim terms of the '725 Patent.

1. "Crystalline monohydrate of the compound of formula (IV)." ('725 patent claims 1, 3, 12).

Construction is required. Despite BMS's assertion that the term "crystalline monohydrate of the compound of formula (IV)" is "well-understood by those of ordinary skill in the art and requires no construction," (BMS Opening Br. at 18), to justify its position, it resorts to relying on extrinsic evidence, including a non-technical dictionary definition of

"monohydrate". (*Id.*) The example the dictionary gives of a "compound, such as calcium chloride monohydrate" is scientifically inaccurate, since $CaCl_2.H_2O$, is not itself an organic compound at all but is a salt. (Desiraju Supp. Decl. ¶¶3-9). But case law confirms that in the pharmaceutical field, terms analogous to "crystalline monohydrate" require construction. *See, e.g.*, *SmithKline Beecham Corp. v. Apotex. Corp.*, 247 F. Supp. 2d 1011 (N.D. Ill. 2003) (construing "crystalline hemihydrate"), *rev'd on other grounds*, 403 F.3d 1331 (Fed. Cir. 2005); *Abbott Labs. v. Sandoz, Inc.*, 486 F. Supp. 2d 767,774 (N.D. Ill. 2007) (construing "crystalline").

Disclaimer by way of product source. During prosecution of the '725 patent, BMS argued at length that the claimed crystalline monohydrate was distinguishable from other forms of dasatinib. (*See* Shannon Decl., Ex. F, '725 patent PH, Dec. 18, 2007 Amendment at 6 ("[The prior art] discloses the compound of formula IV" but "does not disclose that the compound of formula IV, as a monohydrate, would exist in a crystalline form.")). BMS insisted its particular crystal form was patentable due to the inherent unpredictability of prior art processes, which it stated did not allow one of ordinary skill to be able to predict the particular form that would result. (*See* Shannon Decl., Ex. F, '725 patent PH, Dec. 18, 2007 Amendment at 6-7 (APO(Das)016411) ("The Byrn et al. references teaches away from the predictability of forming crystalline monohydrate forms. On page 234, the reference states that 'prediction of crystal structures is not yet generally possible, we must be content with examining the crystal structures of compounds after the fact in looking for explanations of why solvates do or do not form.'"). Based on this representation, the examiner conditioned allowance of the claims on their being limited only to crystal structures made by the specific process disclosed in the specification, *i.e.*, Example 8. (*See* Shannon Decl., Ex. G, '725 patent PH, March 3, 2008 Non-Final Rejection at 4 (APO(Das)016420) ("With this rational [sic] it is clear that the Applicants are entitled to only

[sic] to the crystalline forms that are adequately described in the specific action and are not entitled to a generic crystalline claim …"); *see also* Desiraju Suppl. Decl. ¶ 7). BMS makes no attempt to explain away these clear representations made to the PTO or the examiner's statement reflecting BMS's statements. Thus, BMS is incorrect that Apotex's construction imports a process limitation; instead courts have recognized that where a patentee distinguished its product claims over the prior art on the basis that its product was made with a specific process, the product claims cannot cover products made with a different process. *See AFG Indus., Inc. v. Cardinal IG Co., Inc.*, 224 F. App'x 956, 958-59 (Fed. Cir. 2007) ("It is correct that product claims generally are not limited by how the product is produced. However, exceptions may arise when the product's distinction from the prior art depends on how it was produced, for when the validity of the patent depends on use of a particular process, the claims are construed in the manner that will sustain their validity, when such construction is supported by the record. Thus the process by which a product is produced can limit a product claim when, as here, the process is relied on for patentability and validity.").

Raw material. BMS's citations to intrinsic evidence as well as expert testimony support Apotex, not BMS. BMS recognizes that the '725 patent "discloses an example of the preparation of a crystalline monohydrate in Example 8," which supports Apotex's construction that this term as a whole refers to the particular raw material crystal that results from the process taught in Example 8. (*See* BMS Opening Br. at 18; D.I. 1-5, '725 patent at col. 43, l. 30 – col. 45, l. 32). Example 8 is the only process disclosed in the specification that explains how to create the crystalline monohydrate of the compound of Formula IV. This is why BMS's own expert Dr. Atwood repeatedly invoked Example 8 in attempting to describe the "monohydrate" language:

> Q. Now, when it says, "the monohydrate," is that implying it's the same crystal structure that was prepared by the first part of example 8?

> A. That's my reading of it, certainly. And as I sit here today, I know of only one monohydrate of dasatinib.

(Shannon Supp. Decl., Ex. B, Atwood Tr. 160:22-161:4; *see also id.* 28:21-29:15, 58:12-20, 69:6-19, 90:11-91:6, 115:25-116:21, 163:3-16). Moreover, Dr. Atwood admits that the X-ray powder diffraction ("XRPD" or "PXRD") patterns depicted in the '725 patent can only be obtained from a raw material sample:

> Q. Can you get the result in the top figure of figure 1, the observed PXRD, on anything but a raw material sample?….Q. I'm referring to an API sample, but judges don't necessarily always know what an API is referring to.
>
> A. Okay. Under that proviso, the way to get the top sample is from an API sample….
>
> Q. Right. And similarly, in figure 2, those measurements likewise have to come from API samples, right, or measurements taken on an API?
>
> A. Indeed.

(Shannon Supp. Decl., Ex. B, Atwood Tr. 155:6-156:3; *see also id.* 152:25-153:15).

Covering crystals not produced by BMS's process conditions. Since BMS insisted to the PTO Examiner that the art of growing crystals was "unpredictable," and that a process which worked to produce a monohydrate in the past would not necessarily work to produce the monohydrate crystals here, (Shannon Decl., Ex. F, '725 patent PH, Dec. 18, 2007 Amendment at 6-7 (APO(Das)016411), BMS must be limited to only those crystals and methods for making them that its specification enables the person of ordinary skill to produce. BMS has not enabled any crystalline monohydrate product that differs from those prepared by the '725 patent specification's examples. Thus, BMS cannot expand its claims to cover subject matter it failed to enable. *See, e.g.*, *Digital Biometrics, Inc. v. Identix, Inc.*, 149 F.3d 1335, 1344 (Fed. Cir. 1998) (since a patentee "has the burden to 'particularly point out and distinctly claim the subject matter which the applicant regards as his invention,' 35 U.S.C. § 112, ¶ 2, if the claim is susceptible to a broader and a narrower meaning, and the narrower one is clearly supported by

the intrinsic evidence while the broader one raises questions of enablement under § 112, ¶ 1, we will adopt the narrower of the two."); *Genentech, Inc. v. Wellcome Foundation Ltd.*, 29 F.3d 1555, 1563–65 (Fed. Cir. 1994) (of four possible definitions of claim term "human tissue plasminogen activator" disclosed in specification, adopting only the enabled narrowest one).

BMS does not dispute that a monohydrate has a 1:1 ratio of water to drug in crystalline form. (Shannon Supp. Decl., Ex. B; Atwood Tr. 113:24 – 114:7). As to the disputed aspects of "[c]rystalline monohydrate of the compound of formula (IV)," the construction should clarify it is also a raw material produced by process conditions presented in the specification, with a particular arrangement of the specified compound (Formula IV) in three dimensional space.

2. "… the compound is substantially pure." ('725 patent claim 8, 15, 16).

BMS's proposed construction of "wherein the compound is substantially pure" utterly disregards the ambiguity of this term. To support its construction, BMS assumes that "the compound" really means, "the crystal," and then BMS focuses on a specification statement describing "substantially pure" as "greater than 90 percent." (BMS Opening Br. at 25-26). But BMS fails to explain how to translate the "90 percent" number into a measurable quantity (*e.g.*, by molar ratio, by weight, by volume, elemental analysis, crystallographic purity, etc.).[7] Any understanding of *any* unit of measurement for this term is unsupported by the specification. (Desiraju Supp. Decl. ¶¶ 10-12). BMS's Dr. Atwood conceded as much:

> Q. Where does it say in the specification that it [substantially pure] should be by weight percent as opposed to volume percent or some other measure?
> A. I don't know that it states that.

(Shannon Supp. Decl., Ex. B, Atwood Tr. 142:12-16).

[7] In some instances, weight ratio and molar ratios may produce the same outcome, but only when "pure" refers to crystallographic purity. (Shannon Supp. Decl., Ex. C, Desiraju Tr. 130:24 – 131:8). The '725 patent specification does not make this restriction, and thus one of ordinary skill could not presume identical purity outcomes regardless of measurement method. (Desiraju Supp. Decl. ¶ 11; *see also* D.I. 1-5, '725 patent at col. 15, ll. 31-40).

BMS invokes Dr. Jorgensen to argue there is "no such thing as a 100% pure compound." First, his opinions are inapplicable to the '725 patent.[8] (BMS Opening Br. at 27). Second, he conflates "compound" (*i.e.,* a defined chemical structure) with a composition or substance that contains a compound in varying amounts. Courts "should not rewrite claims to preserve validity." *Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1292 (Fed. Cir. 2006). As written, this claim limitation imposes a purity range on a chemical structure itself, which is nonsensical.

BMS's '725 patent expert, Dr. Atwood, took a different rewriting approach by equating "compound" to mean, "crystalline monohydrate":

> Q. When it talks about substantially pure, … when you see the phrase, "As used herein, substantially pure means a compound having a purity greater than 90 percent," et cetera, ***you're construing a compound there to mean a crystalline form of a compound***?
>
> A. ***Yes. And I'm furthermore construing this to mean the crystalline monohydrate*** having a purity of greater than 90 percent.

(Shannon Supp. Decl., Ex. B, Atwood Tr. 140:25-142:11 (emphasis added)). As Apotex's opening brief explained, claim construction is not the place to rewrite claim language.

BMS's approach also ignores a variety of general claim construction canons. For example, this particular claim limitation uses the definite article "the" to describe the word "compound." This convention necessarily specifies a particularized compound; if it does not, then the claim limitation is indefinite. *See Girafa.com, Inc. v. IAC Search & Media, Inc.*, No. 07-787-SLR, 2009 WL 3074712, at *2 (D. Del. Sept. 25, 2009) (granting summary judgment that claims reciting "*the* home page" were indefinite); *see also Am. Bus Ass'n v. Slater*, 231 F.3d 1, 4–5 (D.C. Cir. 2000) ("[I]t is a rule of law well established that the definite article 'the'

[8] Dr. Jorgensen's expert report did not cover the '725 patent, and any citation to his report to support construction of terms in the '725 patent should be dismissed as beyond the scope of his report. (Shannon Supp. Decl., Ex. A, Jorgensen Tr. 16:18-19). Even so, Dr. Jorgensen conveniently ignores that the '725 patent specification lists a 100% purity characterization as an embodiment. (*Compare* Jorgensen Decl. ¶¶ 8-9 *with* '725 patent at col. 15, ll. 28-30).

particularizes the subject which it precedes."). BMS's construction improperly requires two separate readings of the same term "the compound" within the same claim—one reading to mean crystalline monohydrate, and another reading to mean a composition containing monohydrate. But the same language should be given the same effect in claims. *See, e.g.*, *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1119 (Fed. Cir. 2004); *Frank's Casing Crew & Rental Tools, Inc. v. Weatherford Int'l*, 389 F.3d 1370, 1377 (Fed. Cir. 2004).

Finally, BMS cites two cases in support of its assertion that use of the term "substantially" is common and permitted. (BMS Opening Br. at 27). But neither case is on point. First, *In re Kratz* did not even construe the term "substantially pure." 592 F.2d 1169, 1172 (C.C.P.A. 1979). ("The recitation in the claims of the use of the 'substantially pure' or 'synthetically produced substantially pure' are not seen to influence the conclusions reached. The synthetic or substantially pure compound would be obvious over the natural constituent."). Likewise, *Evans Med. Ltd. v. Am. Cyanamid Co.* is not on point because it dealt with actual purification of a compound, not a description of whether a compound was "substantially pure." No. 98-1446, 1999 WL 594310, at *5-6 (Fed. Cir. Aug. 9, 1999) (unpublished).

For these reasons, Apotex requests that the Court decline to adopt BMS's claim construction and find this term to be insolubly ambiguous, and thus indefinite. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1218 (Fed. Cir. 1991) ("When the meaning of claims is in doubt ... they are properly declared invalid.") (citing *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 453 (Fed. Cir. 1985)).

3. "Which is characterized by an x-ray powder diffraction pattern substantially in accordance with that shown in FIG. 1." ('725 patent claim 1).

BMS's construction changes "substantially in accordance" to "substantially identical." (BMS Opening Br. at 19). This is utterly unhelpful, as "substantially identical" cures no

ambiguities and introduces additional ambiguities. As Dr. Desiraju explained, something is identical or it is not; there are no degrees of identity. (Shannon Supp. Decl., Ex. C, Desiraju Tr. 57:22-60:24). BMS fails to address this linguistic problem with its proposed construction.

Furthermore, BMS ignores that the ambiguity caused by "substantially in accordance" is the undefined term "substantially," which permits limitless variations to a "fingerprint" due to measurement errors and conditions employed. *See Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1286-87 (Fed. Cir. 2009) (XRPD testing "is a method for identifying and distinguishing different crystalline [forms]" that "yields a unique 'fingerprint' for each crystalline form of a chemical" based on size and location of peaks); *see also* Shannon Decl., Ex. F, '725 patent PH, Dec. 18, 2007 Amendment at 7 (BMS stating to PTO that "XRPD of the compounds provides a fingerprint of the spectra for the particular crystalline structure.").

The specification nowhere provides an objective standard for ascertaining "substantial" identity. Although the '725 patent does note that there can be measurement errors, (D.I. 1-5, '725 patent at col. 41, l. 58 – col. 42, l. 13), mere measurement variation was not an approach adopted by BMS's expert Dr. Atwood. Dr. Atwood's position on "substantially identical" borders on the absurd. Notwithstanding the fact that Figure 1 of the '725 patent graphs and traces peaks along both the X axis (peak location) and Y axis (peak height), he contends that as long as the peak *locations* are in the same place, utterly different peak *heights/intensities* will nevertheless constitute samples with PXRD patterns of substantial identity.[9] In *Abbott*, 486 F. Supp. 2d at 775, Dr. Atwood presented a version of this same argument during preliminary injunction proceedings. Judge Andersen rejected Dr. Atwood's assertion that peak heights are

[9] (*See, e.g.*, Shannon Supp. Decl., Ex. B, Atwood Tr. 128:14-19 ("[Y]ou don't have peaks emerging where there is none, and you don't have prominent peaks going away, but rather changes in intensity, and I view that as part of the teaching of the '725, that that means they are substantially—the two patterns would be substantially identical.").

irrelevant in PXRD pattern comparisons, and all that mattered was that some peak "existed", because mere visual inspection showed that the resulting peaks looked "nothing like the features displayed in Figure 1" and would eviscerate the claim language. *Id*.

Dr. Atwood's approach would further render the figure-comparison process utterly subjective, not objective, which is improper. *Cf. Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1353 (Fed. Cir. 2001) (rejecting a patentee's proffered claim construction that depended on the accused infringer's state of mind).

Lacking any support for its construction, BMS cites cases that purportedly construed "substantially," but all are distinguishable. In those cases, the adjective "substantially" was applied to words that permit variability (unlike the term "identical"). *See, e.g.*, *Playtex Products, Inc. v. Proctor & Gamble Co.*, 400 F.3d 901, 908 (Fed. Cir. 2005) (flattened surfaces – "'flattened' requires a comparison between the diametrically opposed surfaces and something"); *Cordis Corp. v. Medtronix AVE, Inc.*, 339 F.3d 1352, 1361 (Fed. Cir. 2003) (uniform thickness). Those cases did not involve precise analytical equipment that produces patterns akin to unique fingerprints for each compound. (Desiraju Supp. Decl. ¶¶ 15, 23).

Finally, BMS's argument that Apotex's construction would write out words from the claim is misleading because it is *BMS* that seeks to remove limitations from the claims it drafted. BMS admitted to the PTO that its crystalline monohydrate of the compound of formula (IV) must have the XRPD pattern of Figure 1. (*See* Shannon Decl., Ex. F, '725 patent PH, Dec. 18, 2007 Amendment at 7 ("XRPD of the compounds provides a fingerprint of the spectra for the particular crystalline structure.")). Permitting variations on the fingerprint necessarily broadens claim scope, contrary to Federal Circuit precedent. *See, e.g.*, *Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418 (Fed. Cir. 1994) (concluding that all of the PXRD peaks, not merely a

subset, had to be affirmatively proven by patentee); *see also Abbott*, 486 F. Supp. 2d at 775 (denying Dr. Atwood's claims that PXRD peaks outside a ± 0.10° peak range was still "a corresponding peak" for infringement and rejecting the premise of ignoring peak heights).

For these reasons, Apotex requests that the Court decline to adopt BMS's construction and find this language insolubly ambiguous, and thus indefinite. *See Amgen*, 927 F.2d at 1218 ("When the meaning of claims is in doubt … they are properly declared invalid.").

4. "Which is characterized by an x-ray powder diffraction pattern (Cu K_α γ = 1.5418 Å at a temperature of about 23° C.) comprising four or more 2θ values selected from the group consisting of: 18.0±0.2, 18.4±0.2, 19.2±0.2, 19.6±0.2, 21.2±0.2, 24.5±0.2, 25.9±0.2, and 28.0±0.2." ('725 patent claim 3).

BMS points to no evidence—intrinsic or extrinsic—to justify its conclusory assertion that this language is "well-understood by those of ordinary skill in the art," an assertion parroted in Dr. Atwood's declaration. (BMS Opening Br. at 24). Unsupported conclusions by experts should be disregarded. *See Aventis Pharm., Inc. v. Barr Labs., Inc.*, 411 F. Supp. 2d 490, 511 (D.N.J. 2006); *Rohm & Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997)).

BMS also does not address the indefiniteness of the term "2θ values" in the context of a Markush group claim format (*see* Section II.A.2 above) and in the context of overbroad variance. (*See* Apotex Opening Br. at 21). A Markush group selection of "2θ values" is an illogical way to characterize a crystal, as Apotex's Opening Brief explained. BMS's expert admitted *every* XRPD pattern for the allegedly patented monohydrate crystals should produce *all eight* listed 2θ values. (*See* Shannon Supp. Decl., Ex. B, Atwood Tr. 98:22-99:5). There is no "selection" of a subset of four that need be made to characterize the crystal. Indeed, doing so means that the claim no longer seeks to incorporate peaks with sufficient precision so that the claim uniquely correspond to monohydrate crystals. Dr Atwood admitted that the four peaks (with variances) listed in claim 3, particularly without any reference to peak intensities as he proposes, are not

unique to dasatinib monohydrate. (*See id.*, Atwood Tr. 90:11-104:8). In fact, Dr. Atwood essentially conceded that other solvate or anhydrate forms could share peak locations due to overlapping ranges permitted by the broad variances of peaks listed for the crystalline monohydrate form. (*Id.*) That is the antithesis of a definite claim that is able to "characterize[]" a sample via an x-ray powder diffraction pattern. *See Amgen*, 927 F.2d at 1218 ("When the meaning of claims is in doubt ... they are properly declared invalid.").

5. "Characterized by unit cell parameters approximately equal to the following: Cell dimensions: a(Å)=13.8632(7); b(Å)=9.3307(3); c(Å)=38.390(2); Volume-4965.9(4) Å^3 Space group Pbca Molecules/unit cell 8 Density (calculated) (g/cm^3) 1.354." ('725 patent claim 5).

BMS does not explain how claim 5's term "characterized by unit cell parameters approximately equal to the following: Cell dimensions: a(Å)=13.8632(7); b(Å)=9.3307(3); c(Å)=38.390(2); Volume-4965.9(4) Å^3 Space group Pbca Molecules/unit cell 8 Density (calculated) (g/cm^3) 1.354" can be applied to anything but a special type of crystal known as a "single crystal". One of ordinary skill in the art would recognize that the values of this claim can only be achieved by a single crystal X-ray diffraction analysis. (Desiraju Supp. Decl. ¶¶ 18-19). Yet, claim 5 depends from claim 3, which refers to a bulk compound raw material sample from which the XRPD data is generated. The two sample types are not the same. It further conflicts with BMS's prior proposal that "compound" mean the crystalline monohydrate sample—but that would necessitate a bulk drug sample for one claim, and a "single crystal" sample for the other. Courts should construe like terms consistently, and when the word "compound" is construed consistently, this term becomes nonsensical. *See, e.g.*, *Innova/Pure Water*, 381 F.3d at 1119; *Frank's Casing Crew*, 389 F.3d at 1377. One of ordinary skill in the art would not understand single crystal and powder diffraction and XRPD to yield necessarily equivalent data, and further would not understand the values provided in this term to be achievable by XRPD at all.

(Desiraju Supp. Decl. ¶ 19).

Even if those deficiencies were overlooked, this claim term still remains insolubly ambiguous with respect to the words "approximately equal." Nowhere does the '725 patent explain how one of ordinary skill in the art is to determine how unit cell parameters can be "approximately equal." Moreover, as with "substantially identical," discussed above, numerical values are equal or they are not; there are no degrees of equality. (*See* Desiraju Supp. Decl. ¶ 7). In fact, the case law cited by BMS, *Quantum Corp. v. Rodime, PLC*, actually found two patent claims invalid where the patentee improperly added the term "approximately" to modify the term "at least 600 tpi" in the reexamination context. 65 F.3d 1577, 1579-80 (Fed. Cir. 1995).

BMS also cites *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1367 (Fed. Cir. 2005), to show that "approximately" can mean "about." But the term "about" neither clears confusion nor removes ambiguity. Moreover, *Merck* is inapplicable here because the parties in *Merck* had stipulated to the term's definition beforehand. What is more, BMS ignores *Amgen*, where the Federal Circuit found invalid claims of a patent for a method of purification of erythropoietin because of the indefinite limitation of "at least about 160,000." 927 F.2d at 1218.

For these reasons, Apotex requests that the Court decline to adopt BMS's claim construction and find this term to be insolubly ambiguous, and thus indefinite. *See Amgen*, 927 F.2d at 1218 ("When the meaning of claims is in doubt ... they are properly declared invalid.").

6. "Which is characterized by differential scanning calorimetry thermogram and a thermogravimetric analysis substantially in accordance with that shown in FIG. 2." ('725 patent claim 2); "[Being further] characterized by a differential scanning calorimetry having a broad peak between approximately 95° C and 130° C"; "Wherein the differential scanning calorimetry further has a peak at approximately 287° C." ('725 patent claims 9, 11, 12).

Instead of proposing constructions that cure ambiguities of these terms, BMS instead suggests that differential scanning calorimetry ("DSC") thermogram and thermogravametric

analysis ("TGA") patterns should be "substantially identical" and that "peaks" or "broad peaks" should exist at "approximately" the temperatures specified. For reasons discussed above, (*see* Section II.B.3), the words "substantially identical" and "approximately" are insolubly ambiguous. Although BMS argues that its constructions account for variations in the testing, (BMS Opening Br. at 23), the Federal Circuit has stated that "[c]laims must reasonably apprise those skilled in the art as to their scope and be as precise as the subject matter permits." *Amgen*, 927 F.2d at 1217 (emphasis added and internal quotations omitted). Yet here, BMS provides no such precision when it uses terms such as "approximately."

Likewise, the patent provides no explanation for the terms "peak" or "broad peak." In fact, Dr. Atwood testified that the relative term "broad peak" requires a scale:

> Q. Do you consider all those peaks there to be broad peaks or narrow peaks or a combination of the two?
>
> A. ... the particular peak, the primary standard could be extraordinarily sharp, or somewhat broad, **depending on the scale** ... So one really would need … a scale in order to assign relative breadth of the peak. ...
>
> Q. Does claim nine of the '725 patent require a particular scale for the peaks?
>
> A. Yes, it does. It does. Because we are referring to the DSC of dasatinib monohydrate, which is figure two.

(Shannon Supp. Decl., Ex. B, Atwood Tr. 59:20 – 60:24 (emphasis added)). But the claim at issue did not invoke Figure 2 as a claim element. Neither does the '725 patent provide such guidance regarding the scale. (Desiraju Supp. Decl. ¶ 26). A person of ordinary skill in the art would thus not be able to understand what "broad peak" means from the patent specification itself, or would be required to import Figure 2 into the claims. (Desiraju Supp. Decl. ¶¶ 26-27).

Dr. Atwood's explanation that broad peak means "a peak associated with the loss of a solvent or water" provides no clarity. One of ordinary skill in the art would recognize that the data from DSC and TGA can only show where water is lost, but cannot clarify whether that water is "water of hydration" or whether the water is residual water, occluded water, etc.

(Desiraju Supp. Decl. ¶ 25). Thus, one of ordinary skill in the art would not be able to confirm whether or not this claim limitation is met.

Likewise, none of these claims explains the precise methodology of the DSC analysis. Although the specification discloses how the inventors themselves conducted their DSC analysis, the claims of the patent are not so limited, but are drafted much more broadly, without limiting the manner in which the DSC analysis is performed. (Desiraju Supp. Decl. ¶¶ 20-22). DSC data vary widely depending on whether the analyses are conducted with open pans, closed pans, pans with pinholes, liquid nitrogen cooling, first runs or second runs. (Desiraju Supp. Decl. ¶¶ 20-22). The failure to specify such parameters makes this term insolubly ambiguous.

As previously discussed above, the two cases cited by BMS, *Quantum* and *Merck*, are distinguishable. *Quantum* found two patent claims invalid where the patentee improperly added the term "approximately" to modify the term "at least 600 tpi" in the reexamination context. 65 F.3d at 1579-80. Meanwhile, *Merck* involved a stipulated definition. 395 F.3d at 1367. *But see Amgen*, 927 F.2d at 1218 ("at least about 160,000" is indefinite).

For these reasons, Apotex requests that the Court decline to adopt BMS's claim construction and find this term insolubly ambiguous, and thus indefinite. *See Amgen*, 927 F.2d at 1218 ("When the meaning of claims is in doubt ... they are properly declared invalid."). To the extent the Court finds this term unambiguous, Apotex requests that this Court construe this term to mean that the product being characterized must match the stated results.

7. "Which corresponds to the loss of one water of hydration on thermogravimetric analysis." ('725 patent claims 9, 12).

BMS's proposed construction of the term "which corresponds to the loss of one water of hydration on thermogravimetric analysis" in the context of the DSC test method adds nothing and ignores the ambiguities introduced by this term. *First*, BMS's construction fails to

acknowledge that the "compound" does not have a ready water molecule available to lose by TGA. (Apotex Opening Br. at 33). BMS presumes "compound" = "crystalline monohydrate."

Second, BMS's approach impermissibly reads out the requirement that the "peak" observed in the DSC results from the loss of "water of hydration." It is black letter law that in claim construction each word should have a meaning. *See In re Gabapentin Patent Litig.*, 503 F.3d 1254, 1263 (Fed. Cir. 2007) (refusing to ignore term "of a mineral acid" from the phrase "anion of a mineral acid"). As even Dr. Atwood conceded, observing a DSC test alone, one of ordinary skill in the art cannot use the test to distinguish between water that originated as water of hydration, surface water, occluded water, etc.:

> If I'm told that there is a weight loss of 3.48 percent, and there is no TGA, I don't what percent of this is surface. I don't know how tightly it's bound. I don't know whether it's in channels, layers or isolated inclathrated sites.

(Shannon Supp. Decl., Ex. B, Atwood Tr. 35:17-22).

For these reasons, Apotex therefore requests that the Court decline to adopt BMS's claim construction and find this term to be insolubly ambiguous, and thus indefinite. *See Amgen*, 927 F.2d at 1218 ("When the meaning of claims is in doubt ... they are properly declared invalid.").

8. "Which is further characterized by a weight loss of 3.48% by [TGA] between 50° C and 175° C." ('725 patent claim 10).

As with claims 9 and 12, discussed above, BMS's proposed construction for the term "which is further characterized by a weight loss of 3.48% by thermogravimetric analysis between 50° C and 175° C" fails to address the fact that the material supposed to lose weight cannot do so without fundamentally changing its structure so that it is no longer "monohydrate". BMS thus mandates test results where a DSC peak correlates to a TGA peak, even though both test methods destroy the very monohydrate crystal structure itself. This is a practical impossibility, because the same crystal cannot be defined through two separately-run tests that both destroy the

sample under analysis. Thus, this language in context is insolubly ambiguous, and thus indefinite. *See Amgen*, 927 F.2d at 1218.

9. "A process for preparing the compound of claim 3." ('725 patent claim 6, 7).

BMS provides the Court with no basis to support its proposed construction of "a process of preparing the compound of claim 3." Indeed, BMS's treatment of this claim term is less than a full sentence, in which BMS impugns Apotex's good-faith positions rather than provide a basis for its own. By its silence, BMS dismisses Federal Circuit precedent that a process claim must occur in the United States to be infringing. *See, e.g., Welker Bearing Co. v. PHD, Inc.*, 550 F.3d 1090, 1095 (Fed. Cir. 2008). Accepting BMS's argument would run contrary to 35 U.S.C. § 271(a), and thus the Court should adopt Apotex's.

10. "The compound of claim [1, 3, or 12]." ('725 patent claims 2, 4, 5, 8, 9, 10, 11, 13, 14, 15, 16).

BMS chose to ignore the improper dependency issues raised by Apotex in its opening brief with respect to claim terms directed to a "compound" of claim 1, 3, or 12. (*See* Apotex opening brief at 34-35). For terms such as "the compound of claim [__]," the definite article "the" is used to describe the word "compound," thereby signifying a particular, specific compound. *See Am. Bus Ass'n*, 231 F.3d at 4–5 ("[I]t is a rule of law well established that the definite article 'the' particularizes the subject which it precedes."). BMS's constructions require varying meanings for "the compound"—sometimes a structure, sometimes "crystalline monohydrate", sometimes a composition—which confirms BMS's constructions cannot be reconciled with one another, rendering the claims insolubly ambiguous and indefinite.

III. CONCLUSION.

For the reasons stated herein, Apotex respectfully requests that the Court adopt Apotex's proposed constructions of the disputed claim terms and phrases.

Respectfully submitted,

SAIBER LLC

_s/ Arnie Calmann_____

Arnold B. Calmann
Geri L. Albin
SAIBER LLC
One Gateway Center
10th Floor, Suite 1000
Newark, New Jersey 07102
(973) 622-3333

William A. Rakoczy
Paul J. Molino
Deanne M. Mazzochi
Tara M. Raghavan
Luke T. Shannon
Roy Chamcharas
RAKOCZY MOLINO MAZZOCHI SIWIK LLP
6 West Hubbard Street, Suite 500
Chicago, Illinois 60654
(312) 222-6301

Attorneys for Defendants Apotex Inc. and Apotex Corp.